PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	19.06.2001
Applicant's or agent's file reference: ICOY/P23098PC	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02497	28/06/2000	30/06/1999

International Patent Classification (IPC) or both national classification and IPC

A61K48/00

Applicant

IMPERIAL COLLEGE INNOVATIONS LIMITED et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☒	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☒	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 30/10/2001.

Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich	Authorized officer / Examiner: Mueller, F
	Formalities officer (incl. extension of time limits)

I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-50 as originally filed

Claims, No.:

1-52 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-19,23-25,43,50-52,

because:

☒ the said international application, or the said claims Nos. 1-19,23-25,43 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☒ no international search report has been established for the said claims Nos. 50-52 (partially).

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,2,4,5,6,7,8,9,12,16,38,39,42,4,46,48,50-52
Inventive step (IS)	Claims	1-52
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II
Priority

The subject-matter of claim 32 which refers to a portion of a c-terminal domain of vErbA,T3R,T3Rbeta1 and T3Ralpha is not entitled to the claimed priority.
Nevertheless the cited document in the International Search Report (Chien et al.,) is not considered as prior art.

Re Item III
Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-16,18,19,25,43 as far as an in vivo method is concerned and claims 17,23 and 24 relate to subject-matter considered by this Authority to be covered by the provision of Rule 67 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

A partial International search was established for the subject-matter of claims 50-52.
The search was restricted to the compounds/methods which were defined by the desired characteristics of suppressing the activity of a selected gene.
Consequently the opinion of this communication is also limited to these features.

Re Item V
Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: GRIGNANI FRANCESCO ET AL: NATURE (LONDON), vol. 391, no. 6669, 19 February 1998 (1998-02-19), pages 815-817,
D2: BEERLI ROGER R ET AL: PROCEEDINGS OF THE NATIONAL ACADEMY

OF SCIENCES OF THE UNITED STATES, vol. 95, no. 25, December 1998 (1998-12), pages 14628-14633, XP002924795 Dec., 1998

D3: HSIEH JAMES J -D ET AL: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 1, 5 January 1999 (1999-01-05), pages 23-28,

D4: WO-A-9923885

D5: WO-A-0041566

2. The subject-matter of independent claim 1 is not novel (Article 33 (2) PCT).

D1 describes a RAR-alpha-PLZF fusion protein which is acting as a repressor on gene transcription of a selected gene(see abstract). The fusion protein is repressing the transcription by acting through modification of chromatin by histone deacetylase (see abstract and p.816, 1.col. 1. and 2. par. and figure 5.b). Experiments on gene expression using this fusion protein were carried out in U397 cells on TGase expression (see figure 4).
All technical features are described in D1 therefore novelty of claim 1 can not be acknowledged.

2.1 The subject-matter of claim 1 is also not novel (Article 33 (2) PCT) over D2.

D2 describes zinc finger-repressor constructs for controlling gene expression. A zinc finger binding domain, recognizing the erbB-2 gene was fused to three domains (KRAB, ERD, SID (mSin3)), see abstract and p. 14628, 2.col. 2. par. The function of sin3 for recruiting and facilitating the generation of a HDAC is considered to be well known in the prior art (see also present application p. 3, l.5-16). The function of these fusion proteins on gene expression and silencing was tested by using a luciferase reporter gene assay in human epithelial cells (see p. 14628, 2.col. 2. par.; p.14632, 2.col. 2. par. Furthermore D2 discusses the use of such fusion proteins in gene therapy for inhibiting the production of viral gene products and for producing gene knockouts transgenic animals (p.14633, 2.col.). Thus the subject-matter of claim 1 is described in D2.

2.2 The subject-matter of independent claim 1 is also not novel (Article 33 (2) PCT over D3.

D3 describes a Gal4-CIR fusion protein (see abstract) which is used over its binding to histone deacetylase and SAP30 for repressing gene expression. The function of this fusion protein as an repressor molecule is tested in HeLa cells by using a CAT-reporter system. (see p. 25, 2.col. 2.par.).Furthermore D3 refers on p. 27, 2.col. ,1.par. in a general statement to the involvement of histone deacetylation in gene repression (reference is also made to sin3, see also item 2.1 above).
Thus all technical features of claim 1 are disclosed in D3 novelty can not be acknowledged.

2.4 The same holds true for the subject-matter of claims 2,4,5,6,7,8,9,12,16,38,39,42, 44,46,48 and 50-52.

2.5 The subject-matter of dependent claims 3,10,11,13-15 and 17-19 are not inventive (Article 33 (3) PCT).
As the general method for suppressing genes by using fusion proteins of a DNA binding domain and a chromatin inactivating protion (e.g. aHDAC recruiting domain) are already disclosed in the prior art (D1-D3) the subject-matter of the claims 3,10,11,13-15 and 17-19 seems not to introduce additional technical features which can be acknowledged as inventive (Article 33 (3) PCT).

3. The subject-matter of independent claim 20 is not novel (Article 33 (2) PCT).
As already laid out, see item 2, fusion proteins consisting of a DNA binding domain and a chromatin inactivating domain are known from the prior art and are used for repressing selected genes (e.g. for knockouts see D2). Thus novelty for claim 20 can not be acknowledged.

3.1 The same holds true for independent claims 21,23,24 and dependent claim 22.

4. The subject-matter of claims 25,26,27,28,29,30,31,32,33,34,35,36,37,40, 41,43,45,47 and 49 is novel (Article 33 (2) PCT).

4.1 The subject-matter of claims 25,26,27,28,29,30,31,32,33,34,35,36,37,40, 41,43,45,47 and 49 is not inventive (Article 33 (3) PCT).

The prior art (D1-D3) already describes fusion proteins consisting of a DNA binding portion and a chromatin inactivation portion which is used for repressing the transcription of selected genes. In addition the prior art already refers to the use of such fusion proteins to selectively knockout genes in transgenic animals (see D2) and their use in neoplastic diseases (see D1, p.817, last par.). In addition D4 describes fusion proteins comprising a Gal4 DNA binding domain and a domain which is operatively associated with histone deactelylase (see claims 10-12, and e.g. figure 3c) for screening of compounds which are modulating nuclear receptor mediated processes (p. 4, l.19-p.5,l.19). Thus the use of these fusion proteins in medicine and their preparation in pharmaceutical compositions as well as their use in bacterial host cells and in transgenic plants are considered not to introduce additional technical features over the prior art which involve an inventive step (Article 33 (3) PCT).

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO0041566	20.07.2000	06.01.2000	12.01.19999

The intermediate document D5 discloses methods for regulating endogenous gene expression by using zinc finger proteins and fusion proteins thereof (see claims 1,5 and 16).

Therefore it could play a role in the national or regional phase (EPO (Article 54(3) EPC) in respect of novelty , namely to claims 1,20,23-32,34,37,44.

Re Item VII

Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2,D3,D4 and D5 is not mentioned in the description, nor are these documents identified therein.